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Missing data in survival analyses

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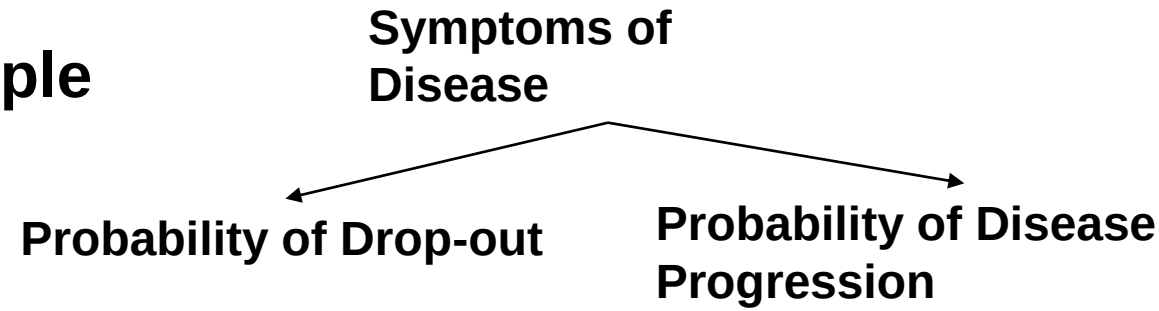
Missing data and Censoring

- At the end of the trial the event of interest may not have been observed
- The patient is censored in the analysis; this is a form of missing data
- There is a sense amongst some investigators that when we censor a patient in the analysis, it solves all the problems
- However traditional survival analysis techniques assume patients are censored at random
- Dependent/informative censoring is problematic to the results and interpretation

Dependent (informative) Censoring

- **Censored subjects are either more or less likely to experience the specific event in the future**
- **In particular, this arises if covariates affect both probability of event and probability of being censored**
- **Example**



- **Data is not missing completely at random**

Examples of censoring that may be dependent (informative)

Blinded independent central review data is missing (investigator thinks patient has progressed and stops further scans. Retrospective BICR does not agree)

Patients take an alternative therapy prior to progression

Analysis of overall survival and cross-over to experimental therapy at the point of disease progression

Patients drop out prior to objective progression because of improvement, or worsening

Time to symptom deterioration – patient progresses radiologically but without symptoms, data collection stopped

Censoring rules impact trial conduct

- Accepted approach for overall survival is to follow all patients to death
- This approach has been advocated for PFS[1]
  - Concern re bias from informative censoring otherwise
- Different approaches also advocated e.g. censor at time of subsequent therapy[2]

[1] **Fleming TR et al: J Clin Oncol. 27:2874-2880, 2009, Carroll KJ: Pharm. Stat. 6:99-111, 2007, CHMP http://www.emea.europa.eu/pdfs/human/ewp/2799408en.pdf**

[2] **Guidance for industry. May 2007. http://www.fda.gov/cder/guidance/7478fnl.htm**

Missing data has been a discussion point for Oncology drug advisory committees (ODACs)

Avastin (breast) ODAC 2010

'The review team did not have confidence in the PFS results because baseline or PFS-determining radiographic scans were missing in 10% of the patients and 34% of the patients were not followed until an IRRC-determined PFS event or the end of the study. …..patients could be offered false hope'

Xgeva (prostate) ODAC 2010

'A *post-hoc exploratory analysis of time to symptomatic bone metastasis, which may be considered a more relevant measure of clinical benefit in this setting, is of limited value due to missing data since most patients were not followed until they experienced the first symptomatic metastasis.'*

Missing data can lead to bias

Censoring analyses co-ordinated by the PhRMA PFS expert team

- 26 trials from 12 companies/institutions re-analysed trials using pre-specified SAP for 5 analyses

  - **Analysis 1- ITT Approach (ITT)**
    - **actual date of progression or death used in the analysis**

  - **Analysis 2- Censor for subsequent therapy (PDT)**
    - **any patient who starts other anti-cancer therapy prior to progressing**

  - **Analysis 3- Censor at treatment discontinuation due to toxicity and other, non-progression related reasons (DISC)**

  - **Analysis 4- Censor missed visits (MV)**
    - **patients who progress or die after ≥2 consecutive missed visits**

  - **Analysis 5- Combined censoring (ALL)**
    - **censored at earliest censoring time of analyses 2 to 4**

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Effect on #events/follow-up from censoring rules

	Median Percentage of ITT Events Censored		Median Percentage Reduction in Follow-up	
Censor	Control	Experimental	Control	Experimental
Subsequent Anti-Cancer Therapy (PDT)	9%	8%	8%	7%
Withdrawal Due to Toxicity /Other non PD reason (DISC)	16%	17%	15%	12%
Two or more Consecutive Missed Visits (MV)	5%	7%	5%	7%
All of the above (ALL)	23%	23%	24%	20%

On average,

- **Censoring discontinuations led to censoring the most events**
- **Censoring was similar across arms**
- **Censoring 'ALL' led to around one quarter of events being censored**

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Differential Informative Censoring (IC)

- Metric defined to represent a measure of degree of IC
- Calculate the Censored Event Rate Ratio (CERR) for each arm
  - CERR=$\frac{\text{event rate* before censoring}}{\text{event rate after censoring}}$
  - If ratio ≠ 1 then evidence of IC within arm
- Ratio(exp/control) of CERR calculated and used as measure of differential IC
- Example: CERR = 2 in exp and 1.5 in control, CERR ratio > 1
  - Would expect experimental to be favoured (in censored analysis) as worse group of experimental patients 'excluded' from censoring

* Event rate = no. of events/total patient follow-up

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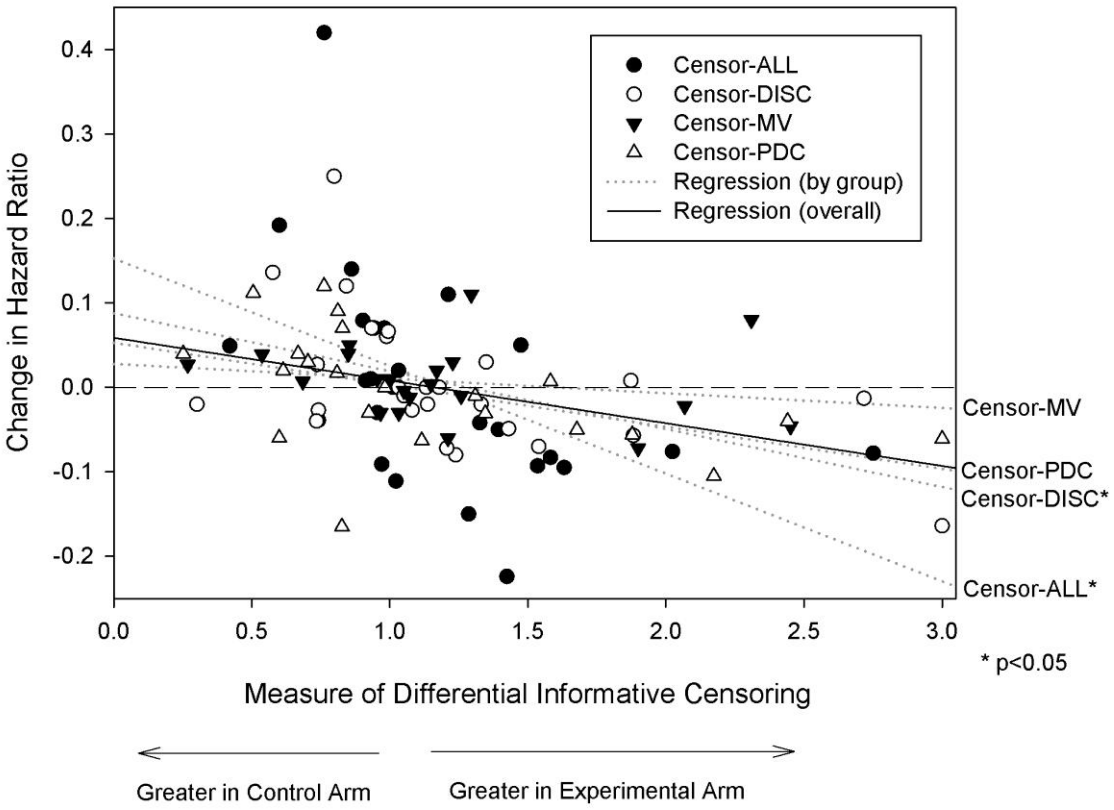
Effect of Differential Informative Censoring



If censoring is related to prognosis in at least one arm AND the extent of IC was higher in exp. arm – then exp. arm favoured by censored analysis

Conclusion from PhRMA work

You need both censoring that is informative and its rate to differ between arms to get bias

Note:
- **95 data points (9 missing due to not estimable rates)**
- **Two x-values >3 and <5 truncated at 3; no impact on slope**

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Pharma Recommendations

- Follow all patients to progression
  - Regardless of whether they stop randomised therapy or start new anti-cancer therapy

- ITT for the primary analysis
  - It is the most conservative
  - Perform supportive analyses which censor on a new anti-cancer therapy
  - The rate of patients who are lost to follow-up should be summarised by treatment arm, both overall and by important prognostic factors

Strategies for dealing with missing data

Strategies for handling missing data

Focus on prevention is key

If all else fails, perform sensitivity analyses:

1) Simple summaries
2) Simple analyses which assign censored patients as events
3) More sophisticated analyses (e.g. multiple imputation methods)

Prevention – some practical steps we can take to minimise missing data

- **Survival: Include in patient consent form that public records can be used to determine date of death**
- **PFS: Plan in protocol to scan until objective progression, irrespective of treatment discontinuation, change of therapy etc**
- **Review metrics during study in a blinded fashion and act on problems**
  - (e.g. number of patients who withdraw prior to progression)

Sensitivity analyses (1)

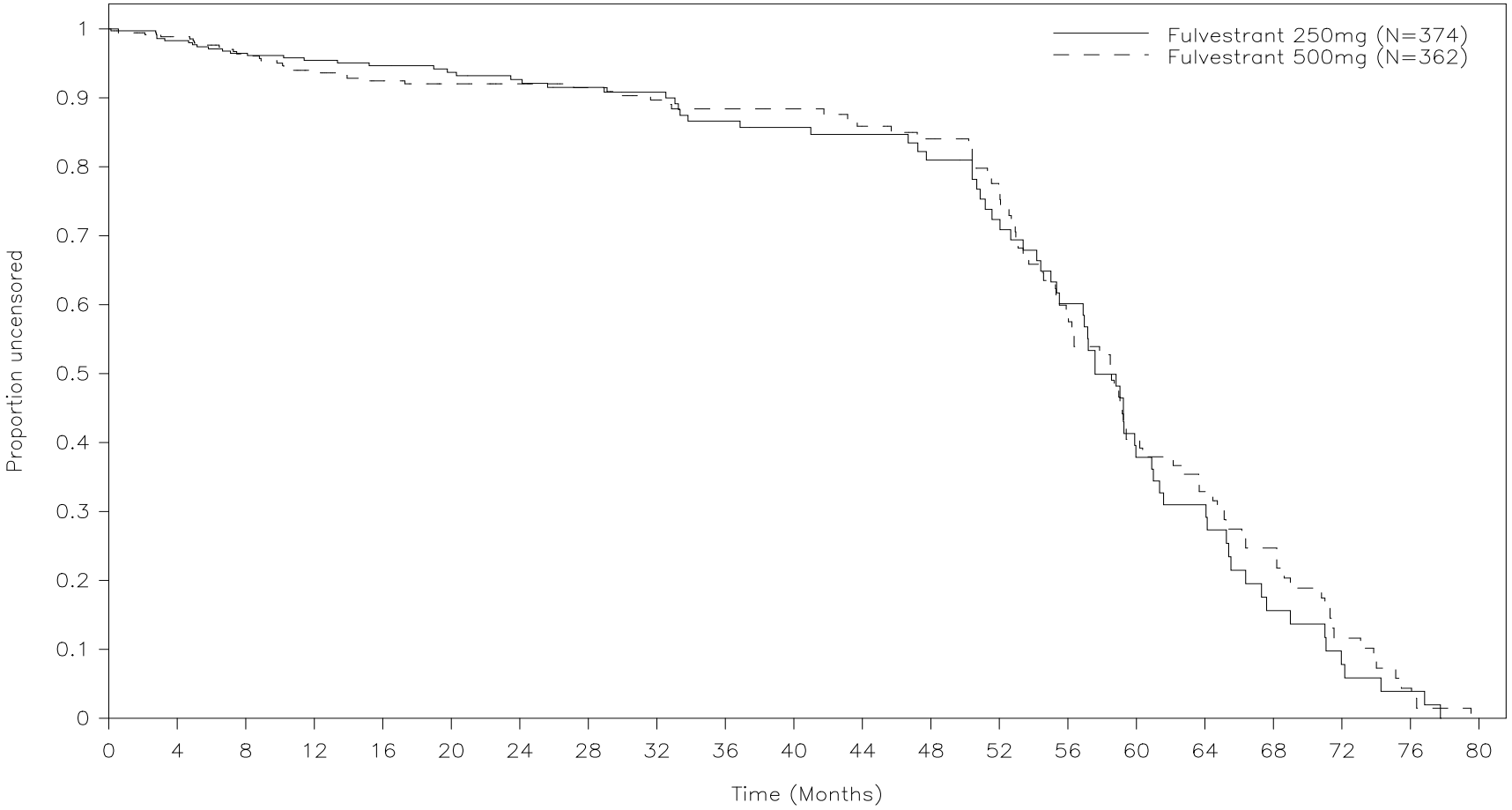
Simple summaries

- Example: missing survival data

- Create a KM plot of time to censoring:
  - An imbalance in patients lost to follow-up could be indicative of bias
  - Similar KM lines indicate similar rates of censoring on each arm

- Summary of censored subjects by time and key baseline factors:
  - The key baseline data should be balanced between the treatment arms for both subjects censored early (e.g. >3m prior to DCO) and late
  - Could also stratify the KM plot of time to censoring by important prognostic categorical variables

Plot of Kaplan-Meier comparison of time to censoring



Conclusion: Time to censoring was comparable between the two treatment groups.

Sensitivity analyses (2)

Example: Assign events to censored patients

- Trial of vandetanib 300mg vs placebo (n=331)
- PFS Hazard ratio=0.46 (95% CI 0.31-0.69) based on blinded independent central review
- 8% vandetanib, 7% placebo progressed by investigator but not by central review >3 months prior to data cut-off
- Censoring of such patients is likely to be informative (Dodd 2008)

- Sensitivity analysis: assumed an event would have occurred according to the central review at the next scheduled visit
- Results for sensitivity analysis: HR=0.51 (95% CI 0.36-0.74)

Sensitivity analyses (3)

"Nonparametric comparison of two survival functions with dependent censoring via nonparametric multiple imputation" Hsu et all, Statist. Med. 2009; 28:462-475

Example

- Primary endpoint: progression free survival
- Secondary endpoint: time to symptom progression
  - Based on patient reported outcome (PRO) data
  - Patient not followed for PRO after radiologic progression
  - Informative censoring likely : would expect radiologic progression to lead to symptom progression

- What imputation method will allow us to get closer to the truth when large amounts of informative censoring prior to DCO?

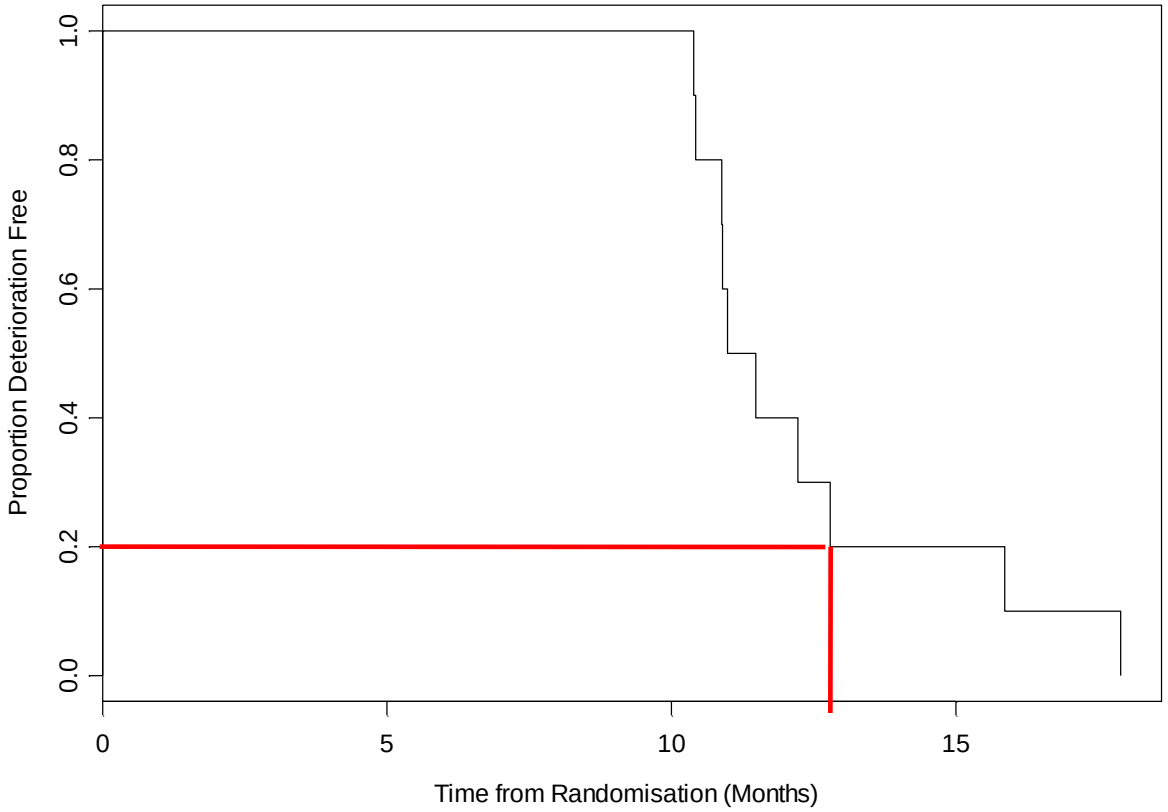
"Nonparametric comparison of two survival functions with dependent censoring via nonparametric multiple imputation" Hsu et all, Statist. Med. 2009; 28:462-475

One possible approach to get closer to truth in analysing time to symptom progression:

- For patients censored – impute a time to event based on "similar" patients with time to event ≥ censored time
- Similar patients - nearest neighbours in terms of risk score for censoring or event of interest
- Risk scores from cox models of time to censoring or time to event with appropriate time dependent covariates
- Eg rate of change in symptom score
- Use Kaplan-Meier imputation to impute a new event time
- Process is repeated for each censored subject
- Analyse data with imputed times to estimate HR adjusted for the presence of informative censoring

Kaplan-Meier Imputation Method

- From NN neighbours, use Kaplan-Meier imputation (KMI) method to read off imputed TTE and censoring indicator

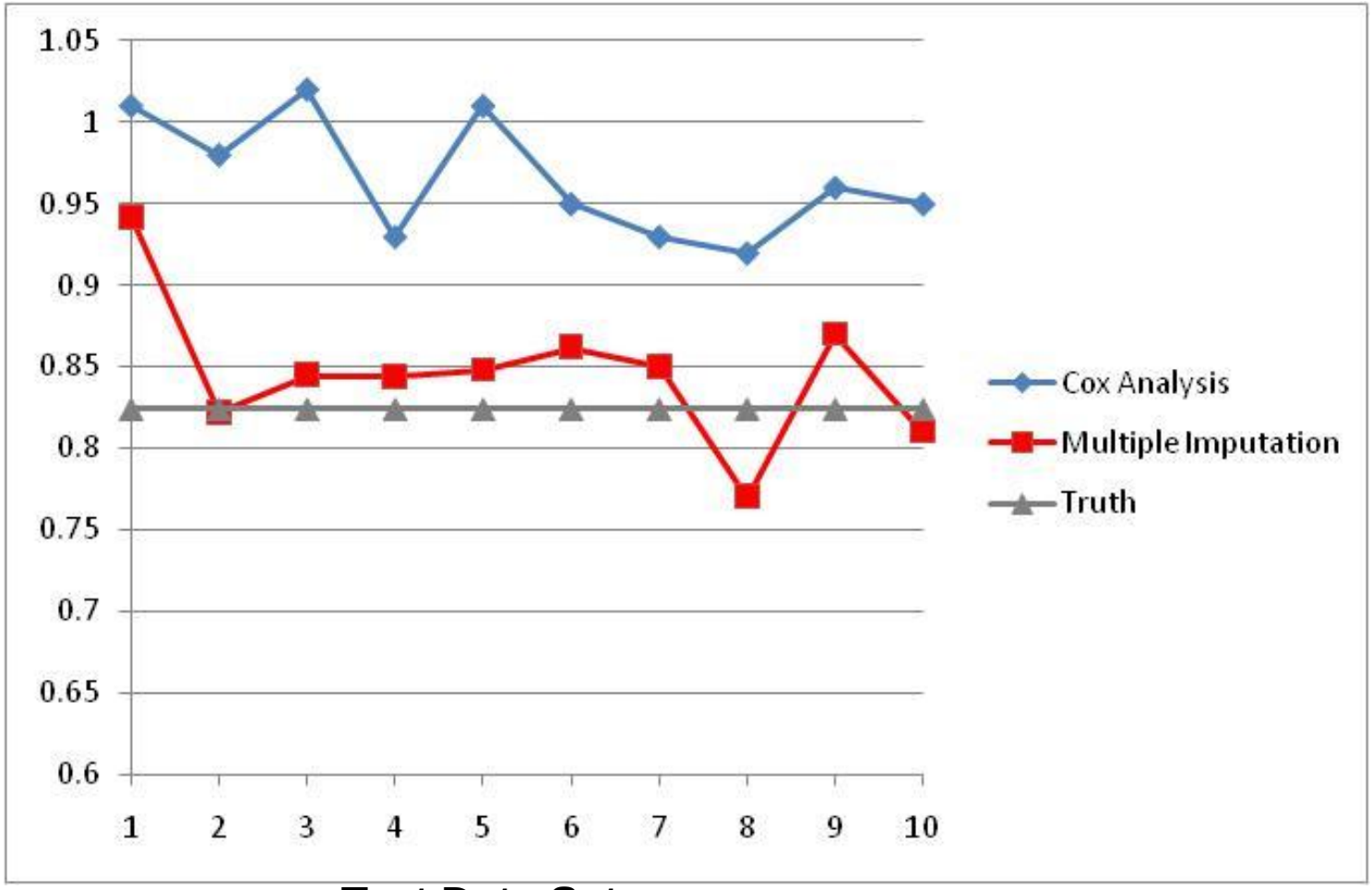


- **Generate random number between 0 and 1 using uniform distribution**
- **Read off KM and impute value for subject i**
  - **E.g. TTE=12.78 mo, event**
- **Nb. Imputed time shouldn't be more than data cut-off date**

Hsu et all, Statist. Med. 2009; 28:462-475

Recovery of Truth In Analysis Of Time To Worsening In LCS Data

Output from Cox Analyses and Multiple Imputation Method



Recovery of Truth In Analysis Of Time To Worsening In LCS Data

- **The hazard ratio returned for the analysis of each test data set is closer to the Truth using the multiple imputation approach vs. the standard cox analysis**

- **Suggests that the auxiliary variable of rate of change in LCS was of use in determining nearest neighbours for Kaplan-Meier imputation**

Summary

Dependent censoring can be problematic to analysis and interpretation of data

Our focus should be on prevention

If all else fails, sensitivity analyses should be performed

1)Simple summaries
2)Simple analyses which assign censored patients as events
3)More sophisticated analyses such as multiple imputation

References

Carroll, K.J. (2007). Analysis of progression free survival in oncology trials: Some common statistical issues. Pharmaceutical Statist 6:99-111

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CHMP. (2008). EMEA/CHMP/EWP/27994/2008. Methodological considerations for using progression-free survival (PFS) as primary endpoint in confirmatory trials for registration

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Dodd (2008). Blinded Independent Central Review of Progression-Free Survival in Phase III Clinical Trials: Important Design Element or Unnecessary Expense? J Clin Oncol. 2008 August 1; 26(22): 3791–3796.

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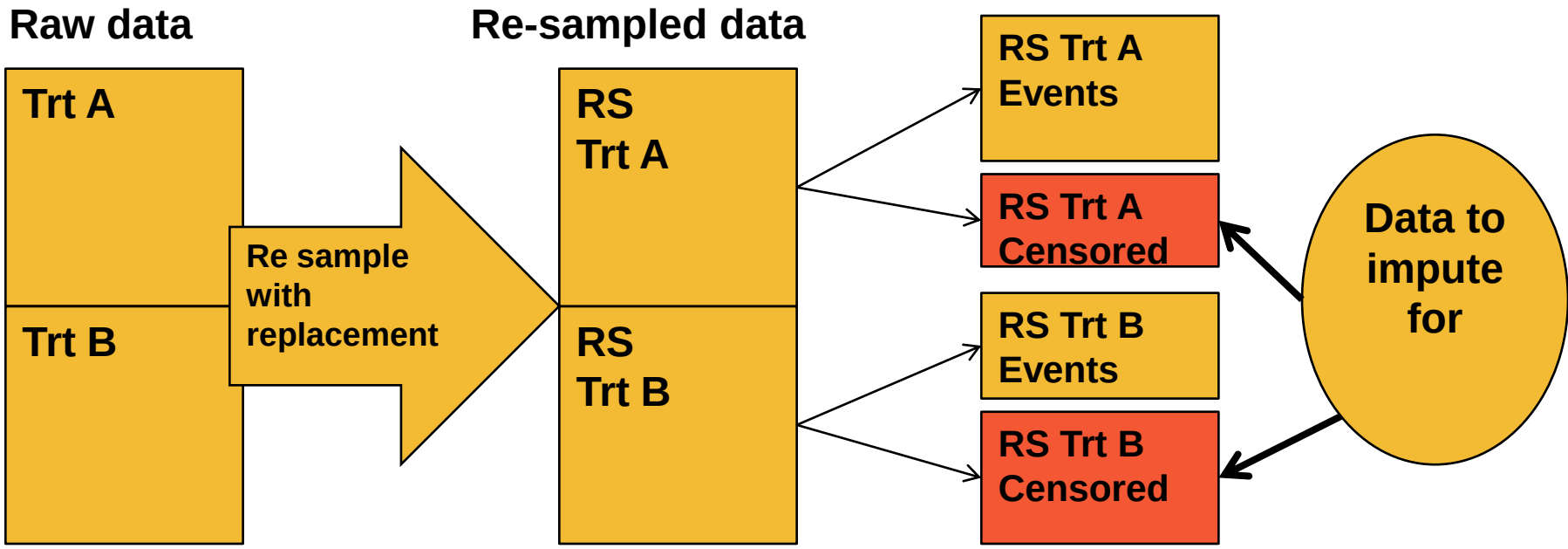
Confidentiality Notice

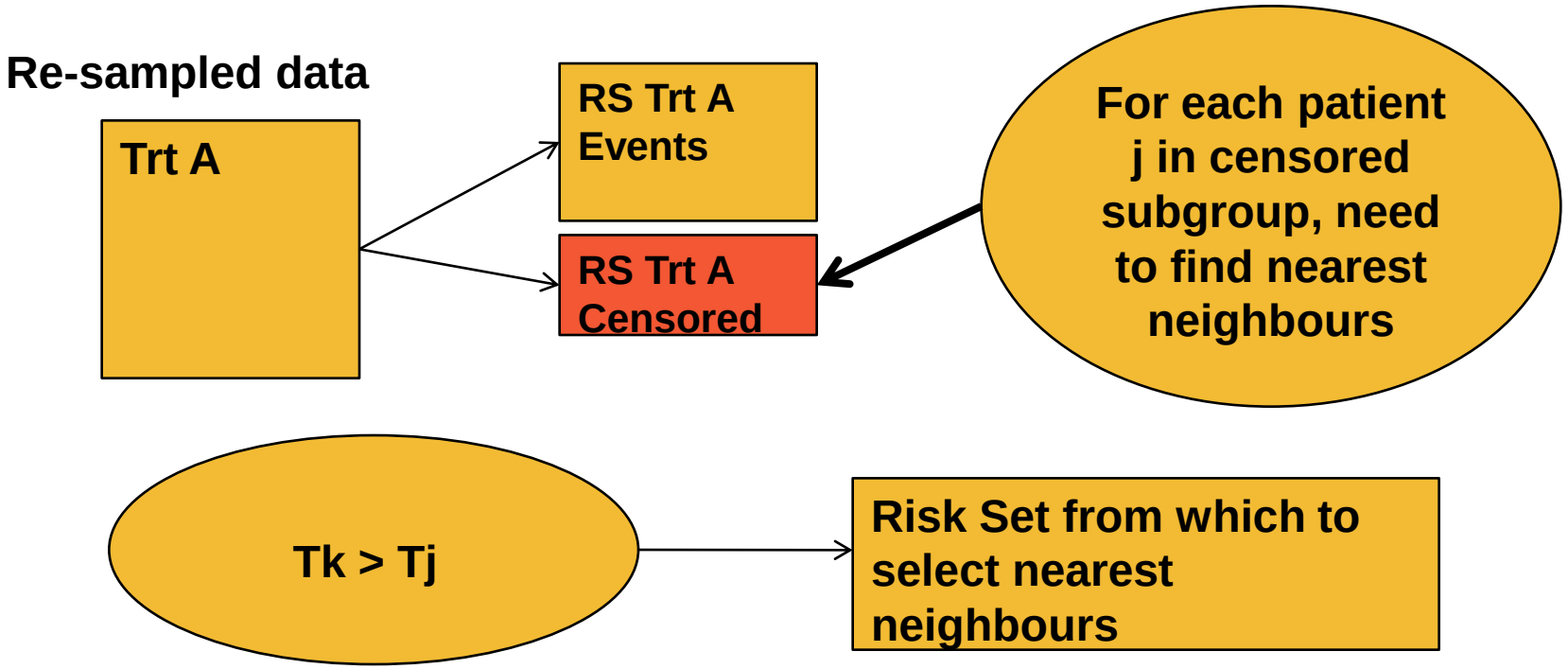
Visual Description of Method



- Randomly re-sample with replacement
- Re-sampled data has same number of observations as the original data in each treatment group

Hsu et all, Statist. Med. 2009; 28:462-475

For censored patients in Trt A



- Nearest neighbours

  - those patients who ‘behave’ most like the censored patient of interest at the time that patient was censored
    - ‘behave’ – prognostic and time dependent covariates

  - selected from those patients who are ‘at risk’ of the event beyond the censored patient of interest

Hsu et all, Statist. Med. 2009; 28:462-475